

What is Claimed is:

1. An oligomeric compound comprising a plurality of 2'-hydroxyl ribonucleosides and having a protected phosphate group at the 5'-terminus.

5 2. An oligomeric compound of claim 1 wherein the 5'-terminus phosphate group is protected by a phosphorus protecting group that is stable extracellularly and labile intracellularly.

10 3. An oligomeric compound of claim 2 wherein the lability is due to intracellular esterases.

4. An oligomeric compound of claim 2 wherein the lability results in removal of the phosphorus protecting group thereby providing the oligomeric compound having a 5'-phosphate intracellularly.

15 5. An oligomeric compound of claim 1 wherein the phosphorus protecting group is (S-acetyl-2-thioethyl) phosphate (SATE).

20 6. An oligomeric compound of claim 1 wherein the protected phosphate group comprises a 7-methylguanosine residue attached to the 5'-position by a triphosphate linkage to give a reverse orientation.

7. An oligomeric compound of claim 6 wherein the 7-methylguanosine residue further comprises an N7 methyl group.

25 8. An oligomeric compound of claim 1 wherein the oligomeric compound is double stranded.

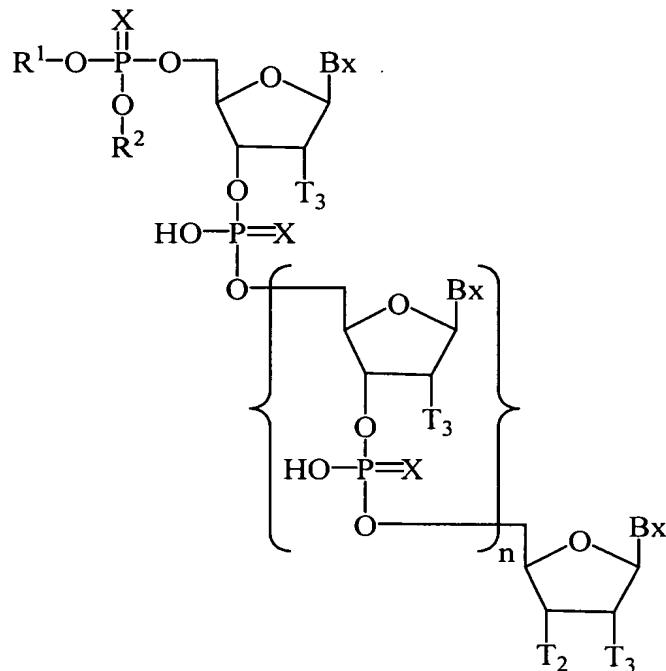
9. An oligomeric compound of claim 8 wherein one strand is an antisense strand.

30 10. An oligomeric compound of claim 8 wherein only one strand comprises the protected phosphate group.

11. An oligomeric compound of claim 10 wherein one strand is an antisense strand, and wherein the antisense strand comprises the protected phosphate group.

12. An oligomeric compound of claim 8 wherein both strands comprise a protected phosphate group.

13. An oligomeric compound of claim 1 having the structure:



10 wherein:

T₂ is a hydroxyl group, a protected hydroxyl group, a sugar substituent group, a conjugate group, a nucleoside, a nucleotide, an oligonucleoside, or an oligonucleotide;

each T₃ is, independently, a hydroxyl group, a protected hydroxyl group, a sugar substituent group, a conjugate group, a nucleoside, a nucleotide, an oligonucleoside, or an oligonucleotide;

15 each X is O or S;

each Bx is an optionally protected heterocyclic base moiety;

n is from 1 to about 50; and

R¹ is H or a phosphorus protecting group and R² is a phosphorus protecting group or

20 R¹ and R² are joined in a phosphorus protecting group.

14. An oligomeric compound of claim 13 wherein at least one T₃ is F.

15. An oligomeric compound of claim 14 wherein at least one T₃ is F and at least one T₃ is a sugar substituent group.

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16. An oligomeric compound of claim 15 wherein T₂ is hydroxyl.

17. An oligomeric compound of claim 15 wherein T₂ is a conjugate group.

10 18. An oligomeric compound of claim 13 wherein R¹ is H and R² is a phosphorus protecting group.

19. An oligomeric compound of claim 18 wherein R² is (S-acetyl-2-thioethyl) phosphate (SATE).

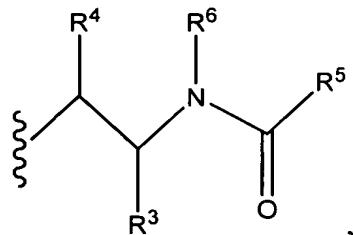
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20. An oligomeric compound of claim 18 wherein R² is straight or branched C₁.C₁₂ alkyl or cyano C₁.C₁₂ alkyl.

21. An oligomeric compound of claim 18 wherein R² is cyanoethyl.

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22. An oligomeric compound of claim 18 wherein R² is a group of formula:



wherein:

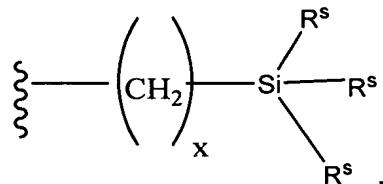
R⁵ is substituted or unsubstituted alkyl, substituted or unsubstituted

25 heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, or substituted or unsubstituted heterocycloalkyl;

R⁶ is R⁵ or H; and

each of R³ and R⁴ is R⁶, or together form a cycloalkyl ring or a heterocycloalkyl ring, each of which is optionally substituted.

23. An oligomeric compound of claim 18 wherein R² is a group of formula:



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wherein:

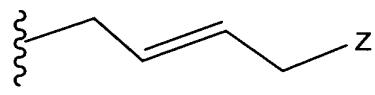
each R^s is, independently, alkyl or aryl; and
x is an integer from 1 to about 12.

- 10 24. An oligomeric compound of claim 23 wherein x is from 1 to about 8.

25. An oligomeric compound of claim 24 wherein x is from 1 to 3.

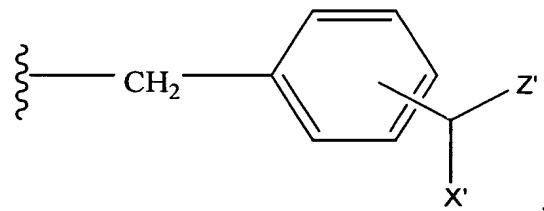
26. An oligomeric compound of claim 18 wherein R² is a group of formula:

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wherein Z is CN, halogen, NO₂, alkaryl, sulfoxy, sulfonyl, thio, substituted sulfoxyl, substituted sulfonyl, or substituted thio.

- 20 27. An oligomeric compound of claim 18 wherein R² is a group of formula:

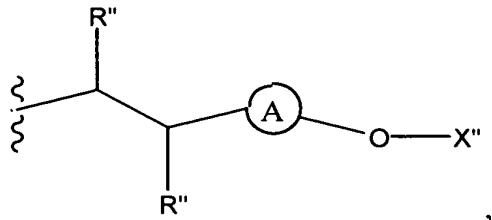


wherein:

Z' is CN, halogen, substituted sulfoxyl, substituted sulfonyl, or a substituted thio group; and

X' is Z' or H.

28. An oligomeric compound of claim 18 wherein R² is a group of formula:



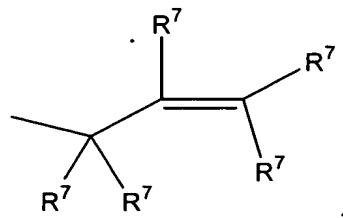
5 wherein:

A is a diradical of a mono- or bi-cyclic aromatic ring system;

X'' is alkaryl, aralkyl, sulfonyl, thio, substituted sulfonyl, substituted thio, or (CO)-R^x, wherein R^x is a substituent or -(CH₂-CH₂)₀₋₁-Si(R^{Si})₃, wherein each R^{Si} is, independently, an alkyl moiety; and

10 each R'' is, independently, H, alkyl, aryl, heteroalkyl, heteroaryl, alkyaryl, or aralkyl or two R'' groups together with the carbon atoms to which they are attached form an optionally substituted aliphatic or aromatic ring system.

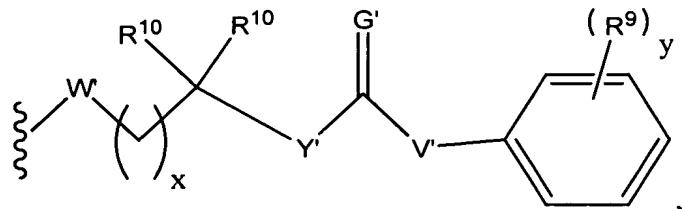
29. An oligomeric compound of claim 18 wherein R² is a group of formula:



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wherein each R⁷ is, independently, H, alkyl, alkenyl, alkynyl, or aryl.

30. An oligomeric compound of claim 18 wherein R² is a group of formula:



20 wherein:

each R¹⁰ is, independently, H, alkyl, alkenyl, alkynyl, or aryl;

W' and G' are each, independently, O or S;

Y' is, independently, O or NR⁸, wherein R⁸ is H, alkyl, alkenyl, alkynyl, cycloalkyl, or phenyl;

V' is, independently, a single bond, O or NR⁸;

5 R⁹ is alkyl, alkenyl, alkynyl, cycloalkyl, CN, NO₂, Cl, Br, I, CF₃, OR⁸, NR⁸R⁸, or phenyl;

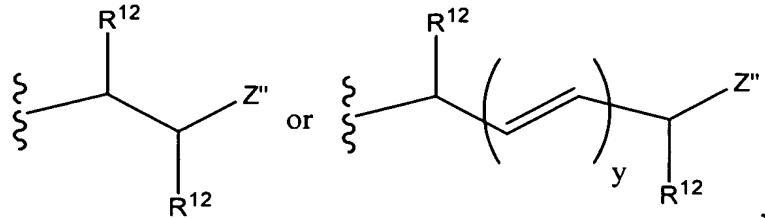
y is 0, 1, 2 or 3; and

x is an integer from 1 to about 12.

10 31. An oligomeric compound of claim 30 wherein x is from 1 to about 8.

32. An oligomeric compound of claim 30 wherein x is from 1 to 3.

33. An oligomeric compound of claim 18 wherein R² is a group of formula:



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wherein:

Z'' is an electron withdrawing group; and

each R¹² is H, substituted or unsubstituted alkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, 20 substituted or unsubstituted aralkyl, or substituted or unsubstituted heterocycloalkyl.

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34. A method of reducing the expression of a nucleic acid molecule encoding a target comprising contacting the nucleic acid molecule with a compound of claim 1, wherein the compound hybridizes with the nucleic acid molecule encoding the target and reduces the 25 expression of the target.

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35. A method of screening for a modulator of a target comprising:

contacting a suitable target segment of a nucleic acid molecule encoding the target with one or more candidate modulators of the target; and

identifying one or more modulators of the target expression which modulate the expression of the target.

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36. A method of claim 35 wherein the modulator of the target expression comprises an oligonucleotide, an antisense oligonucleotide, a DNA oligonucleotide, an RNA oligonucleotide, an RNA oligonucleotide having at least a portion of the RNA oligonucleotide capable of hybridizing with RNA to form an oligonucleotide-RNA duplex, or 10 a chimeric oligonucleotide.

37. A diagnostic method for identifying a disease state comprising identifying the presence of a target in a sample using at least one primer designed to the target, wherein the primer is a compound of claim 1, and wherein the presence of the target indicates the 15 presence of the disease state.

38. A kit or assay device comprising a compound of claim 1.

39. A method of treating an animal having a disease or condition associated with a 20 target comprising contacting the animal with a therapeutically or prophylactically effective amount of a compound of claim 1 so that expression of the target is reduced.

40. A method of reducing the expression of a gene in a biological system expressing the gene comprising contacting the biological system with a composition comprising a 25 compound of claim 1 under conditions effective to reduce the expression of the gene, wherein the compound comprises at least one RNA strand having at least one modified nucleoside, wherein the modified nucleoside has a phosphate precursor moiety.